UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,613	11/16/2004	William A Carter	51-575	7887

23117 7590 07/10/2007
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,613	CARTER ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *April 10, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed April 10, 2007.

Claims 1-7 have been canceled. New claims 8-20 are acknowledged.

Claims 8-20 are pending in the instant application.

Claims 8-20 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed April 10, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Declaration of William A. Carter

Applicant's Declaration of William A. Carter, M.D. is acknowledged and has been fully considered by the Examiner.

Claim Objections

In the previous Office Action mailed December 4, 2007, claim 2 was objected to because the claim contained a typographical error. **This objection is moot** in view of

Applicant's Amendment filed April 10, 2007 to cancel claim 2.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed December 4, 2007, claims 2, 3, 5, and 6 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regarded as the invention. **These rejections are moot** in view of Applicant's Amendment filed April 10, 2007 to cancel claims 2, 3, 5, and 6.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed December 4, 2007, claims 1, 2, and 7 were rejected under 35 U.S.C. 102(b) as being anticipated by Carter, WA [U.S. Patent No. 4,950,652] ('652), made of record on Applicant's information disclosure statement filed June 14, 2004. **This rejection is moot** in view of Applicant's Amendment filed April 10, 2007 to cancel claims 1, 2, and 7.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed December 4, 2007, claims 1-7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carter, WA [U.S. Patent No. 4,950,652] ('652), (made of record on Applicant's information disclosure statement filed June 14, 2004), in view of Ruiz et al. (AIDS, 2001 Vol. 15:F19-F27, made of record on Applicant's information disclosure statement filed June 14, 2004), and Schlomo et al.

(JAMA, 2001 Vol. 285:1155-1163). **This rejection is moot** in view of Applicant's Amendment filed April 10, 2007 to cancel claims 1-7.

Applicant's Amendment necessitated the new grounds of rejection presented below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter, WA [U.S. Patent No. 4,950,652] ('652), (made of record on Applicant's information disclosure statement filed June 14, 2004), in view of Ruiz et al. (AIDS, 2001 Vol. 15:F19-F27, made of record on Applicant's information disclosure statement filed June 14, 2004), and Schlomo et al. (JAMA, 2001 Vol. 285:1155-1163, made of record in the previous Office Action mailed October 10, 2006).

Claims 8 and 15 are drawn to a method of mitigating the adverse effects of antiviral agents in HIV therapy comprising administering to an HIV-infected subject at least one antiviral or anti-retroviral agent until HIV is suppressed, discontinuing antiviral or anti-retroviral therapy, administering a dsRNA, then, when HIV values increase, resuming antiviral or anti-retroviral treatment with at least one antiviral or anti-retroviral agent. Claims 11-14 and 16-20 depend from claims 8 and 15, respectively, and include all the limitations of claims 8 and 15, respectively with the further limitations wherein the dsRNA is administered with said antiviral agent; wherein HIV values are suppressed to a value below detection; wherein the value is less than 50 copies/ml of HIV plasma RNA; wherein two or more anti-retroviral agents are used; wherein the anti-retroviral agent is selected from abacavir, amprenavir, zidovudine, combivir, zalcitabine, lamivudine, didanosine, trizivir, stavudine, lopinavir, efavirenze, nevirapine, indinavir, delavirdine, ritonavir, saquinavir, nelfinvir, and tenofovir, and wherein the dsRNA is rI_n $r(C_{12}U)_n$, Poly A Poly U or rI_n $r(C_{29}G)_n$, in which r is ribo and n has a value of 4 to 29.

'652 teaches and claims a method of treating retroviral disease in a person having HIV comprising administering an antiviral agent in combination with a dsRNA (see Abstract, column 1, lines 57-60, column 2, lines 45-52, column 3, lines 1-4, and claims 4 and 7). '652 also teaches and claims that the dsRNAs are mismatched analogs of complexes of polyriboinosinic and polyribocytydilic acids of the formula rI_n $r(C_{11\text{-}14}U)_n$ and rI_n $r(C_{29}G)_n$ (see column 3, lines 33-50, and claim 4). It is noted that '652 teaches that antiviral drugs were administered alone or in combination with dsRNA (see column 1, lines 57-60 and column 3, lines 1-4).

It is noted that '652 is silent regarding the sequential order of treatment of HIV with the antiviral agent in combination with the dsRNA. For example, '652 does not specify whether the HIV treatment regimen involved "interruption" of the antiviral agent. '652 does also not teach wherein HIV values are suppressed to a value below detection, wherein the value is less than 50 copies/ml of HIV plasma RNA, wherein two or more anti-retroviral agents are used, or wherein the anti-retroviral agent is selected from abacavir, amprenavir, zidovudine, combivir, zalcitabine, lamivudine, didanosine, trizivir, stavudine, lopinavir, efavirenze, nevirapine, indinavir, delavirdine, ritonavir, saquinavir, nelfinvir, and tenofovir.

It is noted that on April 10, 2007, Applicants filed the Declaration of William A Carter, M.D. in which Applicants declared that the method taught by '652 did not involve "interruption" therapy or any point where the antiviral therapy was discontinued then resumed at a later time period.

Ruiz et al. teaches HIV dynamics and T-cell immunity after three structured treatment interruptions in chronic HIV-1 infection (see Abstract). Specifically, Ruiz et al. taught a progressive decrease in viral replication over three structured treatment interruption cycles (see Figures and Conclusions).

Schlomo et al. teaches a triple combination therapy of abacavir, lamivudine, and zidovudine or indinavir, lamivudine, and zidovudine in anti-retroviral-naïve HIV-infected adults (see Context). Specifically, Schlomo et al. teach some patients administered with the abacavir, lamivudine, and zidovudine regimen and some patients administered with the indinavir, lamivudine, and zidovudine regimen exhibited less than 50 copies/ml of

HIV plasma RNA (see Figure 2C).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to devise a method of mitigating the adverse effects of antiviral or anti-retroviral agents in HIV therapy comprising administering to an HIV-infected subject at least one antiviral agent or anti-retroviral agent until HIV is suppressed, discontinuing antiviral therapy, administering a dsRNA, then, when HIV values increase, resuming antiviral or anti-retroviral treatment with at least one antiviral agent using the teachings of '652, and following the teachings and motivation of Ruiz et al. and Schlomo et al.

One of ordinary skill in the art would have been motivated to administer the dsRNA with the antiviral or anti-retroviral agent since '652 taught that certain combination anti-retroviral therapies exhibit synergistic effects. One of ordinary skill in the art would have been motivated to discontinue therapy and then resume therapy since Ruiz et al. taught that treatment interruptions boost immunity and limit virus replication (see Results). Also, Ruiz et al. taught that the positive results of treatment interruption observed in patients provided scientific support for therapeutic strategies of re-exposing the immune system to non-pathogenic formulations of HIV antigens that would eventually better restore protective HIV-1 specific T cell responses. One of ordinary skill in the art would have been motivated to achieve less than 50 copies/ml of HIV plasma because it is well known in the art that this value is considered to indicate a more durable virologic response, indicating successful HIV treatment (see Ruiz et al. at page 1161, last column). One of ordinary skill in the art would have been motivated to

combine two or more antiviral or anti-retroviral agents in combination with a dsRNA for HIV treatment since the prior art taught combination therapy results in less than 50 copies/ml of HIV plasma RNA, indicating successful HIV treatment.

One of ordinary skill in the art would have expected success at devising a method of mitigating the adverse effects of antiviral agents in HIV therapy comprising administering to an HIV-infected subject at least one antiviral or anti-retroviral agent until HIV is suppressed, discontinuing antiviral or anti-retroviral therapy, administering a dsRNA, then, when HIV values increase, resuming antiviral or anti-retroviral treatment with at least one antiviral or anti-retroviral agent since the combined references of '652 along with Ruiz et al. taught the success of such a method of in treating HIV in a human patient. One of ordinary skill in the art would have expected success at using two or more anti-retroviral agents and achieving less than 50 copies/ml of HIV plasma since Ruiz et al. taught the successful use and design of triple combination regimens in treating HIV-infected patients.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

It is noted that a similar rejection was made of record in the Office Action mailed October 10, 2006 against claims 1-7 as being unpatentable over Carter, WA [U.S. Patent No. 4,950,652] ('652), (made of record on Applicant's information disclosure statement filed June 14, 2004), in view of Ruiz et al. (AIDS, 2001 Vol. 15:F19-F27,

made of record on Applicant's information disclosure statement filed June 14, 2004), and Schlomo et al. (JAMA, 2001 Vol. 285:1155-1163).

In response to this rejection, Applicants argue that the claimed invention relates to the use of highly active anti-retroviral therapy followed with strategic therapeutic intervention or interruption. Specifically, Applicants argue that the claimed invention involves the use of highly active anti-retroviral therapy to decrease the HIV load, but before cumulative toxicities develop, the anti-retroviral therapy is stopped (interrupted), during which time a dsRNA, acting as an antiviral agent, is administered and improves the patient's immune system for a period of time. Then, if and when the HIV load increases, the highly active anti-retroviral therapy is resumed. Applicants argue that the Declaration of William A. Carter, M.D. establishes that the prior art reference of the '652 patent did not discontinue anti-retroviral therapy with the dsRNA as instantly claimed, and thus, the '652 patent is combination with Ruiz et al. and Scholomo et al. differs from the instant invention.

These arguments and contentions have been fully considered, but are not found persuasive. First, the Examiner appreciates that Applicants have reiterated their invention as claimed. The Examiner also agrees and acknowledges that the Declaration of William A. Carter, M.D. establishes that the prior art reference of the '652 patent did not discontinue anti-retroviral therapy with the dsRNA as instantly claimed. However, the issue is that the combination of references of the '652 patent, along with Ruiz et al., and Scholomo et al. render the instant claims obvious and demonstrate that, at the time the invention was filed, one of ordinary skill in the art would have been

motivated and expected success at devising a method of mitigating the adverse effects of antiviral agents in HIV therapy comprising administering to an HIV-infected subject at least one antiviral or anti-retroviral agent until HIV is suppressed, discontinuing antiviral or anti-retroviral therapy, administering a dsRNA, then, when HIV values increase, resuming antiviral or anti-retroviral treatment with at least one antiviral or anti-retroviral agent.

For example, as discussed *supra*, '652 clearly teaches and claims a method of treating retroviral disease in a person having HIV comprising administering an antiviral agent in combination with a dsRNA. The issue is that the '652 patent is silent regarding whether or not the antiviral therapy was a continuous or discontinuous regimen. The Declaration of William A. Carter, M.D. has been made of record to establish that the prior art reference of the '652 patent did not discontinue anti-retroviral therapy with the dsRNA. However, the reference of Ruiz et al. provide one skilled in the art the motivation to interrupt therapy for the purpose of providing a degree of immune reconstitution and reducing drug exposure (toxicity). Scholomo et al. was relied upon to teach specific retroviral agents such as abacavir, lamivudine, and zidovudine, for example. Therefore, the combined teachings of '652, in view of Ruiz et al. along with Scholomo et al. demonstrate that the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants also argue that particular studies suggest that structured treatment interruptions are associated with progression of disease and worsening immunologic and virologic clinical outcomes. Applicants point the Examiner to Benson (2006),

Oxenious et al. (2002), and Lawrence et al. (2003), all made of record on Applicant's information disclosure statement filed April 10, 2007.

This argument has been fully considered, but is not found persuasive. While the Examiner acknowledges that some studies, such as those of Benson (2006), Oxenious et al. (2002), and Lawrence et al. (2003) suggest that structured treatment interruptions should be avoided, many other studies suggest the benefit of treatment interruption. For example, the Examiner would like to point Applicant to the references of Lori et al. (The Lancet, 2000 Vol. 354, pages 287 and 288); Aiuti et al. (AIDS, 2003 Vol. 17, pages 2257 and 2258); Bingiovanni et al. (Journal of Antimicrobial Chemotherapy, 2006 Vol. 58:502-505); Moss et al. (Current Drug Targets – Infection Disorder, 2001 Vol. 1:11-17); and Montaner, L. (Trends in Immunology, 2001 Vol. 22: 92-96). In fact, the reference of Benson (2006) provided by Applicant explicitly teaches, "[S]hort term interruptions may be feasible to manage drug toxicities" (see page 111, first column, last paragraph).

In sum, some studies suggest that structured treatment interruptions should be avoided, while other studies suggest the benefit of treatment interruption. The Examiner has provided five references that discuss the benefits of using structured treatment interruptions to control HIV and limit drug exposure. Thus, it is the Examiner's position that the combined teachings of '652, in view of Ruiz et al. along with Scholomo et al. demonstrate that the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
July 4, 2007

/Sean McGarry/
Primary Examiner
AU 1635